Docket No. ALZ-0017-USA-NP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Jao, F., et al.	
Serial No.	:	10/628,970	Technology Center: 1600 Art Unit: 1615
Filed	:	July 28, 2003	Examiner: Pili Asabi Hawes
For	:	FORMULATIONS AND DOSAGE FORMS FOR CONTROLLED DELIVERY OF TOPIRAMATE	

December 22, 2006
(Date)

Mary A. Appollina
Name of applicant, assignee, or Registered Representative

/Mary A. Appollina/
(Signature)

December 22, 2006
(Date of Signature)

ATTENTION: BOARD OF APPEALS AND INTERFERENCES

APPELANTS' BRIEF (37 C.F.R. 41.37)

This is an appeal from the final rejection mailed July 24, 2006, a Notice of Appeal having been mailed on October 24, 2006.

The fees required under 37 C.F.R. 41.20(b)(2), and any required petition for extension of time for filing this brief and fees thereof are addressed with the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief is transmitted as a single copy as per 37 C.F.R. 41.37.

This brief contains these items under the following headings, and in the order set forth below (37 C.F.R. 41.37(c)):

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1. REAL PARTY INTEREST

The real party in interest of the subject patent application is ALZA Corporation, having a principle place of business at 1900 Charleston Road, Mountain View, CA 94043.

2. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences pending.

3. STATUS OF CLAIMS

Claims 31, 33-37 and 48-63 are under appeal in the instant application and stand rejected by the Examiner.

4. STATUS OF AMENDMENTS

No Amendments after Final Rejection have been filed.

5. SUMMARY OF THE INVENTION

The present invention relates to a method for administering high dosages of topiramate to a subject comprising

administering a high dose osmotic dosage form to the subject wherein the dosage form comprises:

(a) a capsule shaped tablet core comprising a plurality of layers wherein a composition containing about 50-60% of topiramate, about 5-15% of a structural polymer carrier and about 15-40% of a solubilizing surfactant is contained in at least one layer and at least one other layer comprises a suitable fluid-expandable polymer;

(b) a semipermeable membrane at least partially surrounding the capsule shaped tablet core to form a compartment having an osmotic gradient to drive fluid from an external fluid environment contacting the semipermeable membrane into the compartment; and

(c) an orifice formed through the semipermeable membrane and into the capsule shaped tablet core to permit the active agent to be released from within the compartment into the external fluid environment;

wherein the dosage form releases the topiramate at a substantially ascending release rate for a prolonged period of time.

The present invention also provides a high dose osmotic dosage comprising:

(a) a capsule shaped tablet core containing a plurality of layers wherein at least one layer comprises about 50-60% of topiramate, about 5-15% of a structural polymer carrier and about 15-40% of a solubilizing surfactant and at least one other layer comprises a suitable fluid-expandable polymer;

(b) a semipermeable membrane surrounding the capsule shaped tablet core to form a compartment having an osmotic gradient to drive fluid from an external fluid environment contacting the semipermeable membrane into the compartment; and

(c) an orifice formed through the semipermeable membrane and into the capsule shaped tablet core to permit topiramate to be released from within the compartment into the external fluid environment.;

which provides a substantially ascending rate of release of the topiramate for a prolonged period of time.

Preferred embodiments of the present invention are as enumerated below:

(a) the dosage form capsule shaped core comprises two layers and the topiramate is contained within a first layer and the fluid-expandable polymer is contained within a second layer and the orifice is formed through the semipermeable membrane adjacent the first layer;

(b) the capsule shaped tablet core comprises three layers and a portion of the topiramate is contained within a first layer and the remaining portion of the topiramate is contained within a second layer, wherein the portion of topiramate contained within the first layer is less than the portion of topiramate contained within the second layer, and

wherein the fluid-expandable polymer is contained within a third layer and the orifice is formed through the semipermeable membrane adjacent the first layer;

(c) the proportion of topiramate contained within the first layer to the topiramate contained within the second layer is within the range of about 1.0:2.0 to about 1.0:1.2;

(d) the proportion of topiramate contained within the first layer to the topiramate contained within the second layer is within the range of about 1.0:1.5 to about 1.0:1.2;

(e) the proportion of topiramate contained within the layers to the solubilizing surfactant is within the range of about 0.5:1.0 to about 2.0:1.0;

(f) the structural polymer carrier is selected from the group consisting Polyox® N80; Polyox® N10; Maltrin M100; polyvinylpyrrolidone (PVP) 12PF; PVP K2932; Klucel EF and Kollidon VA64, preferably, the structural polymer carrier is Polyox® N80;

(g) the solubilizing surfactant is selected from the group consisting of polyethylene glycol (PEG) 3350; PEG 8K; Kollidon K90; Pluronic F 68, F87, F127, F108; Myrj 52S; and PVP K2939, preferably, the solubilizing surfactant is Myrj 52S;

(h) the topiramate is present in an amount equal to about 55%; the structural polymer carrier is Polyox® N80 and is present in an amount equal to about 11.5%; and the solubilizing surfactant is Myrj 52S and is present in an amount equal to about 30%.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL:

6.1 Whether Claims 31, 33-37, 48-56 and 59-61 are unpatentable under 35 U.S.C. §103(a) as obvious over Louie-Helm et al. US 2003/0091630.

6.2. Whether Claims 57, 58, 62 and 63 are unpatentable under 35 U.S.C. §103(a) over Louie-Helm et al. US 2003/0091630 in view of Chen et al. US 6,610,326.

6.3 Whether Claims 31, 33-37 and 48-53 are unpatentable under 35 U.S.C. §103(a) as obvious over Almarsson et al. US 6,699,840.

6.4 Whether Claims 31, 33-37, 48-53, 56-57 and 59-62 are unpatentable under 35 U.S.C. §103(a) as obvious over Almarsson et al. US 6,699,840 in view of Bhatt et al. US 6,368,626.

6.5 Whether Claims 1-53[sic] are unpatentable under 35 U.S.C. §103(a) as obvious over Faour et al. US 6,491,949 in view of Almarsson et al. US 6,699,840.

7. ARGUMENTS:

7.1 Claims 31, 33-37, 48-56 and 59-61 are not obvious under 35 U.S.C. §103(a) over Louie-Helm et al. US 2003/0091630.

In the final rejection of Claims 31, 33-37, 48-56 and 59-61, the Examiner provides the following reasoning for maintaining the rejections under 35 U.S.C. §103(a):

> Louie-Helm discloses a dosage form comprising topiramate, in the form of compressed tablets that contain an erodible swellable matrix along with the active ingredient [0147]. The matrix particles contain 20 wt % Polyox N-60K and 58.07 wt % Polyox N-80, and 0.5 % magnesium stearate [0148]. The swellable erodible matrix is an osmopolymer. Paragraph 0129 discloses binders used in tablet formulations such as polyvinyl pyrrolidone and hydroxymethylcellulose (page 13). The composition comprises between 10-80% drug [0125]. Polyethylene oxide and polyethylene glycol are synonymous. The reference teaches a composition with two polyethylene oxide polymers of differing molecular weights, with the Polyox N-80 having a molecular weight of 200,000 as is claimed in claim 9. Thus Polyox N-80 satisfies the structural polymer limitation. Polyethylene oxide is also a surfactant. Thus the teaching of the use of Polyox N-80 satisfies the limitation of the solubilizing surfactant as well. The reference also teaches the use of another Polyox polymer of a different molecular weight that could also be a solubilizing surfactant. A preferred embodiment of the invention is for the dosage form to be administered once every 24 hours or more [0026].
>
> Although the reference does not disclose the specific amounts as claimed by applicant in the specific ratios as claimed, one of ordinary skill in the art would be able to determine through

routine experimentation the exact percentages and ratios of each ingredient to use in the composition.

Accordingly, it would be obvious to one of ordinary skill in the art at the time the invention was made to prepare an osmotic dosage form comprising topiramate, structural polymers and surfactants and to administer the dosage form once every 24 hours based on the teachings of Louie-Helm.

Appellant submits that the methods and dosage forms of the present invention are directed to high dose, osmotic dosage forms. More specifically, the present invention is directed to high dose osmotic dosage forms wherein the composition comprises about 50-60% topiramate, about 5-15 % structural polymer and about 15-40% solubilizing surfactant and wherein the topiramate is released at a substantially ascending rate of release for a prolonged period of time; and methods which comprising administering high dose osmotic dosage forms wherein the composition comprises about 50-60% topiramate, about 5-15 % structural polymer and about 15-40% solubilizing surfactant and wherein the topiramate is released at a substantially ascending rate of release for a prolonged period of time. By contrast, the dosage forms disclosed in Louie-Helm et al., are swelling, erodible matrix formulations which may be formulated into a tablet or capsule (see for example, the abstract and paragraphs [0013], [0050], [0127], [0138] and Examples 1 and 2), or other form wherein the encapsulating material is highly soluble (see paragraph [0127]). Louie-Helm et al. do not teach or suggest osmotic dosage forms.

Appellants further submit that osmotic dosage forms deliver the active or drug in a different manner than the erodible matrix formulations disclosed by Louie-Helm. More specifically, the osmotic dosage forms of the present invention deliver active or drug as follows. In the gastrointestinal (GI) tract, water is imbibed through the semi-permeable membrane at a controlled rate. This causes the push layer to swell and the drug layer to hydrate, forming a viscous, deformable mass, which is pushed out of the orifice by the expanding push layer (See for example paragraph [0020] of the specification). In contrast, the erodible matrix formulations of Louie-Helm deliver the active or drug by slowly dissolving or eroding the tablet.

Additionally, Louie-Helm et al., do not teach or suggest the specific percentages of topiramate, structural polymer carrier and, solubilizing surfactant required to make the high dose osmotic dosage forms of the present invention.

Appellants therefore submit that in view of the different delivery mechanisms, and the broad ranges of components taught by Louie-Helm et al. it would not be obvious to one skilled in the art to use components and / or percentages of said components as disclosed for an erodible matrix for the formulation of an osmotic dosage form.

Appellants therefore maintain that the teachings of Louie-Helm et al. in US 2003/0091630 do not render obvious Claims 31, 33-37, 48-56 and 59-61.

7.2. Claims 57, 58, 62 and 63 are not obvious under 35 U.S.C. §103(a) over Louie-Helm et al. US 2003/0091630 in view of Chen et al. US 6,610,326.

In the final rejection of Claims 57, 58, 62 and 63, the Examiner provides the following reasoning for maintaining the rejections under 35 U.S.C. §103(a):

> Louie-Helm does not teach specifically Myrj surfactants, but the reference does teach polyoxyethylene glycol.
>
> Chen teaches dosage form comprising an anti-convulsant (divalproex) (abstract). The reference further teaches myrj type surfactants (col. 7, line 60).
>
> Accordingly, it would be obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Louie-Helm with Chen and prepare an osmotic dosage form comprising an anticonvulsant such as topiramate, and surfactants such as myrj because Louie-Helm teaches generically using polyoxyethylene glycol and myrj (taught by Chen) are types of these polymers. There would be sufficient motivation for one of ordinary skill in the art at the time the invention was made to use myrj because Chen teaches that they are surfactants and shows they are useful as polishing agents. The motivation for using surfactants need not be the same as Applicants.

Appellants submits that Claims 54 and 62 are directed to methods and dosage forms, wherein in the high dose osmotic dosage forms the surfactant is Myrj 52S.

Further, Claims 58 and 63 are directed to methods and dosage forms, wherein in the high dose osmotic dosage form, the topiramate is present in an amount equal to about 55%; the structural polymer carrier is Polyox® N80 and is present in an amount equal to about 11.5%; and the solubilizing surfactant is Myrj 52S and is present in an amount equal to about 30%.

The dosage forms disclosed in Louie-Helm et al. are swelling, erodible matrix formulations which may be formulated into a tablet or capsule (see for example, the abstract and paragraphs [0013], [0050], [0127], [0138] and Examples 1 and 2), or other form wherein the encapsulating material is highly soluble (see paragraph [0127]). Louie-Helm et al. do not teach or suggest osmotic dosage forms. Further, Chen et al., disclose a process for preparing divalproex sodium compositions and dosage forms, more particularly dosage forms where the divalproex sodium is not present as an oligomeric structure or a 1:1 molar ratio of sodium valproate to valproic acid, by utilizing neutralized divalproex sodium. The dosage forms disclosed in Chen et al. are tablets, optionally coated with an enteric coating. Chen et al. do not teach or suggest osmotic dosage forms.

Appellants maintain that Louie-Helm et al., and Chen et al., alone or taken together, do not teach or suggest the methods and high dose, osmotic dosage forms of the present invention. Appellants submit that in view of the different delivery mechanisms, it would not be obvious to one skilled in the art to use components and / or percentages of said components as disclosed for an erodible matrix or tablet formulation for preparation of a suitable osmotic dosage form.

Additionally, Appellants submit that as stated by the Examiner, Chen et al. disclose the use of Myrj and other surfactants as polishing agents. Polishing agents as disclosed in Chen are applied to the finished tablet to lubricate the tablets in the polishing step of the manufacturing process. Thus, Appellants understand that the Chen et al. references is being cited by the Examiner solely for the purpose of establishing Myrj as a surfactant. Appellants agree with the Examiner that Myrj is a known surfactant. However, Appellants maintain that there is nothing in the teachings

of Chen et al. to suggest the use of surfactants, Myrj surfactants or Myrj 52S in particular, in a drug layer formulation for use in a high dose, osmotic dosage form.

Appellants therefore maintain that the teachings of Louie-Helm et al. in US 2003/0091630 in view of Chen et al. US 6,610,326 do not render obvious Claims 57, 58, 62 and 63.

7.3 Claims 31, 33-37 and 48-53 are not obvious under 35 U.S.C. §103(a) over Almarsson et al. US 6,699,840.

In the final rejection of Claims 31, 33-37 and 48-53, the Examiner provides the following reasoning for maintaining the rejections under 35 U.S.C. §103(a):

> Almarsson discloses oral dosage forms of topiramate with excipients, such as polyvinyl pyrrolidone and hydroxypropyl methylcellulose (col. 18, lines 13-15, 47, 56-57). The reference also teaches using lubricants like polyethylene glycol (col. 19, line 41). The reference further teaches topiramate controlled release dosage forms, and method for treatment of seizures, epilepsy, tremors, and obesity among others (col. 1, lines 15-18). Such dosage forms are formulated using hydroxypropylmethyl cellulose, and osmotic systems, such as OROS® (Alza Corporation) (col. 21, lines 25-35). The reference teaches the amount of topiramate in the composition can range from 10 mg – 1000 mg (col. 17, line 60-63). The reference further discloses a specific dosage form of their invention to comprise 'a wall defining cavity, the wall having an exit orifice formed or formable therein and at least a portion of the wall being semipermeable; an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall; a dry of substantially dry state drug layer located within the cavity adjacent the exit orifice and in direct or indirect contacting relationship with the expandable layer; and a flow promoting layer interposed between the inner surface of the wall an at least the external surface of the drug layer located wit tin the cavity, wherein the drug layer comprises a salt of the topiramate' (col. 22, line 29-44). Claim 25 recited a method for delivering high doses of topiramate by administering the composition for claim 22. Since the composition of claim 22 is anticipated by this reference, the method is also anticipated by this

reference since the method step of administering the composition is a necessary step in the method of treating seizures, epilepsy, and tremors disclosed in the reference. The limitation 'for delivering high doses' is an intended use and dose not hold patentable weight since the claim is dependent on a composition claim that does not recite any amount of topiramate, high or low. The method of enhancing bioavailability by administering the topiramate composition of claim 22 would be an inherent property of the composition when it is administered to a patient in need thereof. In order to treat seizures, epilepsy or tremors the composition would need to be administered to a person suffering from said diseases. Thus upon administration for the treatment of these ailments the bioavailability would also be increased.

Although the reference does not specifically disclose the particular percentages of each ingredient, one of ordinary skill in the art would be able to determine through routine experimentation the amounts of each ingredient to add in the composition. One of ordinary skill in the art would be motivated to increase the amount of active agent in the composition because the composition is intended for one-a-day controlled release of the active ingredient. Therefore it would have been obvious to one or ordinary skill that the amount of active agent in such a composition would need to be greater then the amount in a dosage form that is intended for multiple administration within a 24 hour period. Once the amount of the active ingredient is determined based on the amount necessary to treat the medical condition being treated, and based on the average patients gender, age, and weight, then the amount of the structural polymer and the solubilizing surfactant can be adjusted to optimize the formulation. The release rate is another property that can be modified based on the amount of the structural polymer and the solubilizing agents added. Thus any release profile desired can be achieved via routine experimentation to select optimum levels of each ingredient. The generic invention is embodied and described in Almarsson.

The Examiner further responds to Appellants previous arguments as follows:

Applicants argue that Almarrason does not teach the specific percentages of topiramate, surfactant, and structural polymer as claimed by Applicant. Almarrason teaches using 10-1000 mg of topiramate. Applicants have not shown that this teaching does not satisfy the percentage requirement in the instant claims.

> Furthermore, such a wide range of dosage amount for the active ingredient taught by Almarrason would provide sufficient motivation to one of ordinary skill in the art to optimize through routine experimentation the amount of each ingredient to make the desired dosage form. From the teachings it is apparent that using high doses of topiramate is envisioned. It would be obvious to one or ordinary skill in the art to adjust the amounts of the solubilizing surfactant and the structural polymer based on the amount of active agent to make a dosage form with the desired controlled release characteristics. Thus routine experimentation would lead one of ordinary skill in the art to arrive at the percentages as claimed, because Alamarrason teaches using high doses of topiramate.

Appellants respectfully submit that Claims 22 and 25 mentioned by the Examiner in his arguments above are no longer pending in the present application and no Claim currently pending or under appeal herein is dependent from Claim 22 or 25.

The currently appealed rejection is directed to Claims 31, 33-37 and 48-53 which claims are directed to high dose osmotic dosage forms wherein the composition comprises about 50-60% topiramate, about 5-15 % structural polymer and about 15-40% solubilizing surfactant and wherein the topiramate is released at a substantially ascending rate of release for a prolonged period of time; and methods which comprising administering high dose osmotic dosage forms wherein the composition comprises about 50-60% topiramate, about 5-15 % structural polymer and about 15-40% solubilizing surfactant and wherein the topiramate is released at a substantially ascending rate of release for a prolonged period of time.

Appellants submit that Almarsson et al. do not teach or suggest the specific percentages of topiramate, structural polymer carrier and, solubilizing surfactant required to make the high dose osmotic dosage forms of the present invention. Rather Almarsson et al. generically disclose pharmaceutical compositions and dosage forms, including oral dosage forms, controlled and delayed release dosage forms, parenteral dosage forms, topical, transdermal and mucosal dosage forms which dosage forms may be formulated with topiramate salts as the active ingredient. (col 16, line 39 through col. 24, line 63) Further, Almarrson et al. do not teach any specific dosage forms.

Appellants further submit that in the present invention it was unexpectedly found that the use of about 15-40% solubilizing surfactant permits the formulation of topiramate, a low solubility drug, at the high loading levels of 50-60%, thereby permitting the formulation of the high dosage forms of the present invention. Almarsson et al. teach and disclose salts of topiramate, the formulation of said salts in dosage forms, including OROS® and the use of said salts and dosage forms for the treatment of seizures, epilepsy, tremors and other diseases. Almarsson et al. disclose dosage forms comprising topiramate (as opposed to topiramate salts), in only a single, generic statement (col. 10, lines 43-57) and further specify that the preferred form is one whose solubility is at least greater than 10 mg/mL. Appellants further submit that the topiramate salts disclosed by Almarsson et al. have a high solubility, for example, for the sodium trihydrate salt, Almarsson et al teach a solubility of 1.33 g/mL (which equals 1,330 g/L or 1,330 mg/mL) in water and 1.47 g/mL (which equals 1,470 g/L or 1,470 mg/mL) in methanol. In contrast, the solubility of topiramate in water is listed in Chemical Abstracts as 0.032 g/L (which equals 0.032 mg/mL) at 25°C, pH7. Appellants maintain that because of the large (~5 orders of magnitude) difference in solubility between topiramate and topiramate salts, it would not be within the scope of routine experimentation for one of ordinary skill in the art to formulate topiramate in a high dose osmotic dosage form, based on the generic disclosure in dosage forms in Almarsson et al.

Appellants therefore maintain that the teachings of Almarsson et al. in US 6,699,840 do not render obvious Claims 31, 33-37 and 48-53.

7.4 Claims 31, 33-37, 48-53, 56-57 and 59-62 are not obvious under 35 U.S.C. §103(a) over Almarsson et al. US 6,699,840 in view of Bhatt et al. US 6,368,626.

In the final rejection of Claims 31, 33-37, 48-53, 56-57 and 59-62, the Examiner provides the following reasoning for maintaining the rejections under 35 U.S.C. §103(a):

Almarsson discloses oral dosage forms of topiramate with excipients, such as polyvinyl pyrrolidone and hydroxypropyl methylcellulose (col. 18, lines 13-15, 47, 56-57). The reference also teaches using lubricants like polyethylene glycol (col. 19, line 41). The reference further teaches topiramate controlled release dosage forms. Such dosage forms are formulated using hydroxypropylmethyl cellulose, and osmotic systems, such as OROS® (Alza Corporation) (col. 21, lines 25-35). The reference teaches the amount of topiramate in the composition can range from 10 mg – 1000 mg (col. 17, line 60-63). The reference further discloses a specific dosage form of their invention to comprise 'a wall defining cavity, the wall having an exit orifice formed or formable therein and at least a portion of the wall being semipermeable; an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall; a dry of substantially dry state drug layer located within the cavity adjacent the exit orifice and in direct or indirect contacting relationship with the expandable layer; and a flow promoting layer interposed between the inner surface of the wall an at least the external surface of the drug layer located wit tin the cavity, wherein the drug layer comprises a salt of the topiramate' (col. 22, line 29-44). The reference also incorporates by reference US6368626 (Bhatt), which teaches the specific dosage form, which Almarsson suggested to be adapted for use with topiramate.

Bhatt teaches the same surfactants and structural polymers as claimed by Applicant (col 12, lines 46-67, col. 13, lines 1-15). The reference also discloses a push layer comprising osmopolymers (col. 14, lines 5-25). The reference teaches a drug loading between 20-90% by weight (col. 6, line 57). The reference discloses the use of a structural polymer between 1-90% off the composition, specifically 20.3 % Polyox N-80 (see example1, line 26). The drug layer of the prior art is the center core of the dosage form, see Figure 1A. Example 3 discloses 20.24% Polyox N-80, 3% polyoxy 40 stearate (Myrj 52S), 2% PVP, and 63.67 % polyethylene oxide in the push layer (col. 22, lines 25-35). The reference teaches a core comprising a drug composition and a push layer compositing an osmopolymer. The dosage form also possesses a semipermeable wall and an exit orifice. The comprising language of the instant claims does not exclude the flow promoting interior wall also present in the dosage form of the prior art. The reference discloses in Example 1 the composition contains approx. 30% surfactant and 69% active agent. This is a ratio of approx. 1:2. One of ordinary skill in the art would be able to determine through routine experimentation the reasonable amount of surfactant to add to maintain the desired ratio and achieve the desired release profile.

It would be obvious to one of ordinary skill to use the dosage form disclosed by Bhatt to make a controlled release osmotic dosage form of topiramate because Almarsson suggests and teaches to do so.

The Examiner further responds to Appellants previous arguments as follows:

> Applicants argue that Almarrason does not teach the specific percentages of topiramate, surfactant, and structural polymer as claimed by Applicant. Almarrason teaches using 10-1000 mg of topiramate. Applicants have not shown that this teaching does not satisfy the percentage requirement in the instant claims. Furthermore, such a wide range of dosage amount for the active ingredient taught by Almarrason would provide sufficient motivation to one of ordinary skill in the art to optimize through routine experimentation the amount of each ingredient to make the desired dosage form. Form the teachings it is apparent that using high doses of topiramate is envisioned. It would be obvious to one or ordinary skill in the art to adjust the amounts of the solubilizing surfactant and the structural polymer based on the amount of active agent to make a dosage form with the desired controlled release characteristics. Thus routine experimentation would lead one of ordinary skill in the art to arrive at the percentages as claimed, because Alamarrason teaches using high doses of topiramate.
>
> Furthermore Bhatt is relied upon for teaches[sic] that high dose amounts of active ingredient in osmotic dosage forms are known in the art. Additionally, Bhatt teaches the structural polymers and surfactants that are claimed in the instant application. A combination of the two references would lead one of ordinary skill in the art to the claimed dosage form, and the amounts could be arrived upon based on routine experimentation.

Claims 31, 33-37 and 48-53 are directed to high dose osmotic dosage forms wherein the composition comprises about 50-60% topiramate, about 5-15 % structural polymer and about 15-40% solubilizing surfactant and wherein the topiramate is released at a substantially ascending rate of release for a prolonged period of time; and methods which comprising administering high dose osmotic dosage forms wherein the composition comprises about 50-60% topiramate, about 5-15 % structural polymer and about 15-40% solubilizing surfactant and wherein the topiramate is released at a substantially ascending rate of release for a prolonged period of time.

Appellants submit that Almarsson et al. do not teach or suggest the dosage forms or methods of the present invention and further do not teach or suggest the specific percentages of topiramate, structural polymer carrier and, solubilizing surfactant required to make the high dose osmotic dosage forms of the present invention. Rather Almarsson et al. generically disclose pharmaceutical compositions and dosage forms, including oral dosage forms, controlled and delayed release dosage forms, parenteral dosage forms, topical, transdermal and mucosal dosage forms which dosage forms may be formulated with topiramate salts as the active ingredient. (col 16, line 39 through col. 24, line 63) Further, Almarrson et al. do not teach any specific dosage forms.

Appellants further submit that Bhatt et al. do not teach or suggest the dosage forms or methods of the present invention and further do not teach or suggest the specific percentages of topiramate, structural polymer carrier and, solubilizing surfactant required to make the high dose osmotic dosage forms of the present invention. Rather Bhatt et al. disclose push-stick osmotic dosage forms, wherein the drug layer is released in a dry or substantially dry form (i.e. in plug form). Appellants submit that the use of about 15-40% solublizing surfactant, as is claimed in the present invention, promotes dissolution and suspension of the topiramate for optimal performance (see for example, paragraph [00018], [00023] and [00088] of the specification). Thus, in the present invention, the drug layer containing the topiramate is dissolved and / or suspended when released from the dosage form, and is not released in a dry or substantially dry form, as would be suggested by Bhatt et al. Additionally Bhatt et al. does not teach or suggest an osmotic dosage form wherein the drug layer is released in a substantially ascending rate of release for a prolonged period of time; rather the dosage forms disclosed by Bhatt et al. have a uniform release rate.

Thus Appellants submit that one skilled in the art, in reading Bhatt et al., either alone or in combination with Almarsson et al., would not be motivated to make the high dose osmotic dosage forms of the present invention. Appellants further submit that, because of the generic nature of the Almarsson disclosure and the uniform release rate (rather than substantially ascending release rate) disclosed by Bhatt et al., the specific

percentages of topiramate, structural polymer carrier and, solubilizing surfactant required to make the high dose osmotic dosage forms of the present invention would not be within the scope of routine experimentation.

Finally, Appellants submit that in the present invention it was unexpectedly found that the use of about 15-40% solubilizing surfactant permits the formulation of topiramate, a low solubility drug, at the high loading levels of 50-60%, thereby permitting the formulation of the high dosage forms of the present invention. Although Bhatt et al. discloses a long list of drugs, including anticonvulsants, which may be formulated within the push-stick osmotic dosage forms, Bhatt et al. does not teach or suggest formulations or dosage forms comprising topiramate as the active agent. Additionally, Almarsson et al. teach and disclose salts of topiramate, the formulation of said salts in dosage forms, including OROS® and the use of said salts and dosage forms for the treatment of seizures, epilepsy, tremors and other diseases. Almarsson et al. disclose dosage forms comprising topiramate (as opposed to topiramate salts), in only a single, generic statement (col. 10, lines 43-57) and further specify that the preferred form is one whose solubility is at least greater than 10 mg/mL. Appellants further submit that the topiramate salts disclosed by Almarsson et al. have a high solubility, for example, for the sodium trihydrate salt, Almarsson et al teach a solubility of 1.33 g/mL (which equals 1,330 g/L or 1,330 mg/mL) in water and 1.47 g/mL (which equals 1,470 g/L or 1,470 mg/mL) in methanol. In contrast, the solubility of topiramate in water is listed in Chemical Abstracts as 0.032 g/L (which equals 0.032 mg/mL) at 25°C, pH7. Appellants maintain that because of the large (5 orders of magnitude) difference in solubility between topiramate and topiramate salts, it would not be within the scope of routine experimentation for one of ordinary skill in the art to formulate topiramate in a high dose osmotic dosage form, based on the generic disclosure in dosage forms in Almarsson et al.

Appellants therefore maintain that the teachings of Almarsson et al. US 6,699,840 in view of Bhatt et al. US 6,368,626 do not render obvious Claims 31, 33-37, 48-53, 56-57 and 59-62.

7.5 Claims 1-53[sic] are not obvious under 35 U.S.C. §103(a) over Faour et al. US 6,491,949 in view of Almarsson et al. US 6,699,840.

Appellants wish to point out that Claims 1-30, 32 and 38-47 are no longer pending in the present application and no Claim currently pending or under appeal herein is dependent from any of Claims 1-30, 32 and 38-47.

In the final rejection of Claims 1-53[sic], the Examiner provides the following reasoning for maintaining the rejections under 35 U.S.C. §103(a):

> Faour discloses an osmotic dosage delivery device that comprises a core, the core comprises a first drug and a second drug. The first and second drug are enclosed in a semipermeable membrane (col. 1, lines 40-53). The first and second active ingredients are the same (col. 1, line 57). The first and second active agent containing devices have different rates of release (col, 1, line 58-63). Differences in the rates of release of the same active ingredient is achieved via the type and amount of semipermeable membrane material used as well as the type and amount of other excipients, such as structural polymers and osmoagents (col. 5, line 18-33). The reference further discloses the use of an osmopolymer in the core of the first osmotic device and the coating of the second osmotic device (col. 5, lines 33-33). The reference discloses types of osmopolymers or swellable hydrophilic polymers (col. 6, lines 61-67 and col. 7, lines 1-22). The reference teaches discloses[sic] the delivery device comprises and exit means or passageway (col. 4, line 8). The reference discloses the use of surfactants such as poloxamers, polyvinyl pyrrolidone, etc (col. 11, lines 10-20). The reference discloses a composition that will provide a 'substantially ascending' rate or release and drug plasma concentration because the reference teaches the device will deliver up to 100% of the drug over a period of 18-24 hours. As the semipermeable membrane breaks down and the drug is release the rate of release will increase and as the amount of drug released increases so will the drug plasma concentration.
>
> Figure 1 discloses the composition in which the first drug layer surrounded by the semipermeable coating is contained with in the second drug layer surrounded by a second semipermeable coatings, and a exit orifice is present. Instant claims do not specify how the first and second drug compositions are in communication

in the core of the delivery device. The reference discloses that this type of delivery device is suitable for use with a wide variety of drugs, of those drugs, neuroleptics are listed. Topiramate is a neuroleptic drug.

One of ordinary skill would be able to determine through routine experimentation the desired percentages of first and second drug and desired ratio of surfactant to drug in the composition.

Faour teaches the structural limitations of the dosage form with the exception of the particular active ingredient.

Almarsson teaches the use of topiramate in an osmotic delivery device...

It would have been obvious to one of ordinary skill in the art to make an osmotic delivery device offering controlled release of an active substance such as topiramate, with a core that contains a first and second drug composition comprising the same active substance with different release profiles because Faour teaching this technology and Almarsson suggests making controlled release dosage forms comprising topiramate and further suggest using osmotic delivery devices.

The Examiner further responds to Appellants previous arguments as follows:

Applicants argue that a combination of Almarrason and Faour does not teach the specific percentages of topiramate, surfactant, and structural polymer as claimed by Applicant. Alamarason teaches using 10-1000 mg of topiramate. Applicants have not shown that this teaching does not satisfy the percentage requirements in the instant claims. Furthermore, such a wide range of dosage amount for the active ingredient taught by Almarrason would provide sufficient motivation to one or ordinary skill in the art to optimize through routine experimentation the amount of each ingredient to make the desired dosage form. From the teaching it is apparent that using high doses of topiramate is envisioned. It would be obvious to one or ordinary skill in the art to adjust the amounts of the solubilizing surfactant and the structural polymer based on the amount of active agent to make a dosage form with the desired controlled release characteristics. Thus routine experimentation would lead one of ordinary skill in the art to arrive at the percentages claimed, because Alarrason teaches using high doses of topiramate. Faour teaches the structural limitations of the dosage form with the exception of the particular active ingredient. Thus one of ordinary skill in the art would be motivated from the

combination of the two references to make an osmotic dosage (taught by Faour) from comprising a high dose amount of topiramate (taught by Almarrason).

Appellants submit that Faour et al., in US 6,491,949 disclose a dual osmotic device comprising a first osmotic device enclosed within a second osmotic device wherein the first drug layer and the second drug are separated by a semi-permeable membrane and wherein the rate of release of the first drug layer and the rate of release of the second drug layer are achieved by differences in the type and amount of semi-permeable layer present. In additionally disclosed embodiments, Faour et al. teach that the chemical and physical integrity of the first and / or second semi-permeable membrane is lost, thereby controlling the rate of release of the osmotic device. Appellants submit that Faour et al. do not teach or suggest the high dose osmotic dosage forms of the present invention, wherein the drug layer comprises about 50-60% topiramate and about 15-40% solubilizing surfactant and wherein the topiramate is released with a substantially ascending rate of release over a prolonged period of time, without the use of a semi-permeable membrane which controls the release rate of the drug by loss of it chemical and physical integrity.

Appellants further submit that one skilled in the art in reading Faour et al. and Almarsson et al., either alone or in combination, would not be motivated to make the claimed dosage forms containing the specified percentages of topiramate and solubilizng surfactant. Appellants submit that neither Almarsson et al, nor Faour et al., teach or suggest the specific percentages by weight of the topiramate and the solubilizing surfactant present in the high dose osmotic dosage forms of the present invention.

Appellants further submit that topiramate is a low solubility drug and that in the present invention it was unexpectedly found that for administration of high doses of topiramate, formulating the drug containing composition with about 15-40% solubilizing surfactant results in enhanced solubility of the topiramate so as to permit formulation of the dosage form for high doses, with a substantially ascending release rate for a prolonged period of time (see for example, paragraphs [00023], [00088] and [00100] of the specification). Appellants submit that Almarsson et al. disclose the formulation of

topiramate (as opposed to topiramate salts), in only a single, generic statement (col. 10, lines 43-57) and further specify that the preferred form is one whose solubility is at least greater than 10 mg/mL. Appellants additionally submit that the topiramate salts disclosed by Almarsson et al. have a high solubility, for example, for the sodium trihydrate salt, Almarsson et al teach a solubility of 1.33 g/mL (which equals 1,330 g/L or 1,330 mg/mL) in water and 1.47 g/mL (which equals 1,470 g/L or 1,470 mg/mL) in methanol. In contrast, the solubility of topiramate in water is listed in Chemical Abstracts as 0.032 g/L (which equals 0.032 mg/mL) at 25°C, pH7. Appellants maintain that because of the large (5 orders of magnitude) difference in solubility between topiramate and topiramate salts, it would not be within the scope of routine experimentation for one of ordinary skill in the art to formulate topiramate in a high dose osmotic dosage form, based on the generic disclosure in dosage forms in Almarsson et al. Appellants further maintain that Faour et al. do not teach or suggest how the component percentages should be adjusted to formulate a low solubility active ingredient such as topiramate. Appellants therefore maintain that it would not be obvious to one of ordinary skill in the art in reading Faour et al. and Almarsson et al., either alone or in combination, and further, to make the high dose osmotic dosage forms of the present invention, through routine experimentation.

Appellants therefore maintain that the teachings of Almarsson et al. US 6,699,840 in view of Faour et al. US 6,491,949 do not render obvious Claims 31, 33-37, 48-53, 56-57 and 59-62.

7.6 Conclusion:

For the foregoing reasons, reversal of the rejections relating to Claims 31, 33-37 and 48-63 is respectfully requested.

Appellants acknowledge that there is an outstanding rejection of Claims 31, 33-37 and 48-63 under the judicially created doctrine of obviousness-type double patenting over Claims 1-34 of co-pending Application No 11/024329; an outstanding rejection of Claims 1-53[sic] under the judicially created doctrine of obviousness-type double

patenting over Claims 1-21 of co-pending Application No. 11/0243330; and an outstanding rejection of Claims 31, 33-37 and 48-63 under the judicially created doctrine of obviousness-type double patenting over Claims 1-27 and 32-39 of co-pending Application No. 11/024378. Appellants respectfully submit that they will be able to address these rejections upon an indication that the pending claims are otherwise deemed to be in condition for allowance.

8. CLAIMS APPENDIX:
(See Attached)

9. EVIDENCE APPENDIX:
(See Attached)

10. RELATED PROCEEDINGS APPENDIX:
(See Attached)

Respectfully submitted,
/Mary A. Appollina/

_____
Mary A. Appollina
Attorney for Applicants, Reg. No. 34,087

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
(732) 524-3742
Dated: December 22, 2006

Attachments

APPENDIX OF CLAIMS

31. A method for administering high dosages of topiramate to a subject comprising:

administering a high dose osmotic dosage form to the subject wherein the dosage form comprises:

(a) a capsule shaped tablet core comprising a plurality of layers wherein a composition containing about 50-60% of topiramate, about 5-15% of a structural polymer carrier and about 15-40% of a solubilizing surfactant is contained in at least one layer and at least one other layer comprises a suitable fluid-expandable polymer;

(b) a semipermeable membrane at least partially surrounding the capsule shaped tablet core to form a compartment having an osmotic gradient to drive fluid from an external fluid environment contacting the semipermeable membrane into the compartment; and

(c) an orifice formed through the semipermeable membrane and into the capsule shaped tablet core to permit the active agent to be released from within the compartment into the external fluid environment;

wherein the dosage form releases the topiramate at a substantially ascending release rate for a prolonged period of time.

33. The method according to Claim 31, wherein the capsule shaped tablet core comprises two layers and the topiramate is contained within a first layer and the fluid-

expandable polymer is contained within a second layer and the orifice is formed through the semipermeable membrane adjacent the first layer.

34. The method according to Claim 31, wherein the capsule shaped tablet core comprises three layers and a portion of the topiramate is contained within a first layer and the remaining portion of the topiramate is contained within a second layer, wherein the portion of topiramate contained within the first layer is less than the portion of topiramate contained within the second layer, and wherein the fluid-expandable polymer is contained within a third layer and the orifice is formed through the semipermeable membrane adjacent the first layer.

35. The method according to Claim 34, wherein the proportion of topiramate contained within the first layer to the topiramate contained within the second layer is within the range of about 1.0:2.0 to about 1.0:1.2.

36. The method according to Claim 34, wherein the proportion of topiramate contained within the first layer to the topiramate contained within the second layer is within the range of about 1.0:1.5 to about 1.0:1.2.

37. The method according to Claim 34, wherein the proportion of topiramate contained within the layers to the solubilizing surfactant is within the range of about 0.5:1.0 to about 2.0:1.0.

48. A high dose osmotic dosage form comprising:

(a) a capsule shaped tablet core containing a plurality of layers wherein at least one layer comprises about 50-60% of topiramate, about 5-15% of a structural polymer carrier and about 15-40% of a solubilizing surfactant and at least one other layer comprises a suitable fluid-expandable polymer;

(b) a semipermeable membrane surrounding the capsule shaped tablet core to form a compartment having an osmotic gradient to drive fluid from an external fluid environment contacting the semipermeable membrane into the compartment; and

(c) an orifice formed through the semipermeable membrane and into the capsule shaped tablet core to permit topiramate to be released from within the compartment into the external fluid environment.;

which provides a substantially ascending rate of release of the topiramate for a prolonged period of time.

49. The dosage form according to Claim 48, wherein the capsule shaped tablet core comprises two layers and the topiramate is contained within a first layer and the fluid-expandable polymer is contained within a second layer and the orifice is formed through the semipermeable membrane adjacent the first layer.

50. The dosage form according to Claim 48, wherein the capsule shaped tablet core comprises three layers and a portion of the topiramate is contained within a first layer

and the remaining portion of the topiramate is contained within a second layer, wherein the portion of topiramate contained within the first layer is less than the portion of topiramate contained within the second layer, and wherein the fluid-expandable polymer is contained within a third layer and the orifice is formed through the semipermeable membrane adjacent the first layer.

51. The dosage form according to Claim 50, wherein the proportion of topiramate contained within the first layer to the topiramate contained within the second layer is within the range of about 1.0:2.0 to about 1.0:1.2.

52. The dosage form according to Claim 50, wherein the proportion of topiramate contained within the first layer to the topiramate contained within the second layer is within the range of about 1.0:1.5 to about 1.0:1.2.

53. The dosage form according to Claim 50, wherein the proportion of topiramate contained within the layers to the solubilizing surfactant is within the range of about 0.5:1.0 to about 2.0:1.0.

54. The dosage form as in Claim 48, wherein the structural polymer carrier is selected from the group consisting Polyox® N80; Polyox® N10; Maltrin M100; polyvinylpyrrolidone (PVP) 12PF; PVP K2932; Klucel EF and Kollidon VA64.

55. The dosage form as in Claim 48, wherein the structural polymer carrier is Polyox® N80.

56. The dosage form as in Claim 48, wherein the solubilizing surfactant is selected from the group consisting of polyethylene glycol (PEG) 3350; PEG 8K; Kollidon K90; Pluronic F 68, F87, F127, F108; Myrj 52S; and PVP K2939.

57. The dosage form as in Claim 48, wherein the solubilizing surfactant is Myrj 52S.

58. The dosage form as in Claim 48, wherein the topiramate is present in an amount equal to about 55%; the structural polymer carrier is Polyox® N80 and is present in an amount equal to about 11.5%; and the solubilizing surfactant is Myrj 52S and is present in an amount equal to about 30%.

59. The method as in Claim 31, wherein the structural polymer carrier is selected from the group consisting Polyox® N80; Polyox® N10; Maltrin M100; polyvinylpyrrolidone (PVP) 12PF; PVP K2932; Klucel EF and Kollidon VA64.

60. The method as in Claim 31, wherein the structural polymer carrier is Polyox® N80.

61. The method as in Claim 31, wherein the solubilizing surfactant is selected from the group consisting of polyethylene glycol (PEG) 3350; PEG 8K; Kollidon K90; Pluronic F 68, F87, F127, F108; Myrj 52S; and PVP K2939.

62. The method as in Claim 31, wherein the solubilizing surfactant is Myrj 52S.

63. The method as in Claim 31, wherein the topiramate is present in an amount equal to about 55%; the structural polymer carrier is Polyox® N80 and is present in an amount equal to about 11.5%; and the solubilizing surfactant is Myrj 52S and is present in an amount equal to about 30%.

APPENDIX OF EVIDENCE

"none"

RELATED PROCEEDINGS APPENDIX

"none"